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(54) **SYSTEM FOR DEMAND-BASED ADMINISTRATION OF INSULIN.**

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JP-A-54 110 699
US-A-2 690 178
US-A-3 604 417
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US-A-4 055 175
US-A-4 078 562
Münch. med. Wschr. Vol. 121(1979), p. 821-824
Bioelectrochemistry and Bioenergetics Vol. 15 (1978), p. 607-624
An Implantable Artificial Pancreas, W. Schubert et al, Med. & Biol. Engineering & Comput, 1980, vol.18, p. 527-537

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Description

This invention relates to a system for the administration of insulin to a patient in response to his or her insulin requirements, which system comprises an insulin dispenser for the infusion of insulin into a patient, transducer means responsive to a property of a body fluid of the patient and adapted to generate a signal having a magnitude which is a function of that property, and dispenser control means to receive the signal and operably associated with the dispenser so as to deliver insulin to the patient in response to the received signal.

Diabetes mellitus is a disease characterised by hyper-glycemia, polyuria, and wasting. Hyperglycemia is due to decreased utilization of glucose and also increased production of glucose. The discovery of insulin in 1922 has made it possible to control the blood glucose level in diabetic patients, at least partially. This has enhanced the well-being and survival of diabetic patients. However, recent studies indicate that long term complications of diabetes such as blindness, heart failure, kidney failure, neuropathy and vascular disease are not completely obviated by insulin therapy and that better glucose control is necessary.

To improve the control of glucose levels, several methods have been suggested. Among such methods are the "close control" method whereby a patient is hospitalized with attendant frequent assays of blood sugars and frequent insulin injections (e.g., before each meal). To effect control, the individual or the clinical laboratory has to perform frequent blood sugar analyses on a regular basis.

A further extension of the aforementioned treatment by "close control" is the use of a continuous or constant rate infusion of insulin using an insulin dispenser for infusion of this hormone into the patient. With such a machine, the rate of insulin administration must be predetermined by a physician, and further requires the maintenance of a steady diet and a continued uniform sensitivity of the patient to insulin.

It has been proposed to use a sensor responsive to the patient's glucose level for regulating the rate of insulin administration by the aforementioned insulin dispenser. However, all glucose sensors proposed to date have been unstable *in vivo* when used for time periods in excess of several weeks and thus are not very practical. A variety of problems have been encountered with such sensors: (1) Sensors that rely on the oxidation of glucose (with glucose oxidase) exhibit stability problems due to the inherent instability or inactivation of such enzymes, (2) sensors relying on the direct oxidation of glucose (by means of electrodes) encounter undesirable polarization phenomena on the electrode surfaces, (3) the *in vivo* period of reliability of heretofore known implanted glucose sensors is shortened by fibrous or fibrinous encasement. This is so because all heretofore known glucose sensors are rate-dependent. That is, the glucose concentration in a patient's blood is indicated by the reaction rate of glucose at the sensor. Glucose in the blood must diffuse to the electrode or to the enzyme present in the sensor. For reliable sensor signal output, a constant mass transfer resistance of glucose to the sending element must be maintained. Progressive fibrous or fibrinous encasement of the sensing element continuously alters such resistance and requires frequent recalibration of the sensor.

An example of prior insulin infusion systems is shown in US—A—4,055,175. This system incorporates a direct sensor for ascertaining the blood glucose concentration. It suffers, however, from one or more of the disadvantages pointed out above in connection with glucose sensors generally.

It is therefore an aim of the present invention to provide a system which overcomes these disadvantages, and according to the invention a system of the character set forth in the opening paragraph of the Specification is characterised by transducer means which are responsive to the osmolality, or a colligative physical property which changes in proportion to the osmolality, of a body fluid.

It is found that such sensing of a body fluid of a patient permits a far more accurate control to be exercised over the supply of insulin to a patient than in the prior systems mentioned above.

A preferred transducer means for the purpose of the present invention is an implantable blood or tissue fluid osmolality sensor or detector, e.g., an implantable osmometer that generates an electrical, mechanical or telemetry signal which, in turn, controls the operation of the insulin dispenser. Another embodiment would have a primary transducer sensing osmolality and one or more secondary transducers sensing electrolytic conductivity or ion concentration. A preferred insulin dispenser is a portable unit which can be worn by the patient or implanted in the patient, and includes an insulin reservoir, a pump means, and a switch means responsive to the signal or signals from one or more sensors or detectors and controlling the delivery of insulin.

In another preferred embodiment, an implanted sensor is used in conjunction with a dual channel catheter and has a shape enabling the sensor or sensors to be either (a) removed and replaced or (b) removed, cleaned of fibrinous or other material, and replaced through a channel in the catheter other than the channel carrying insulin to the patient.

Insulin from the reservoir can be delivered to the patient intraperitoneally, intravenously, or subcutaneously, or by any other convenient means as desired.

Brief description of the drawings

In the drawings,

Figure 1 is graphical correlation of blood glucose level and blood osmolality in normal and diabetic mammals;

Figure 2 is a graphical representation of the effect of endogenous insulin on various mammalian blood parameters;

Figure 2a is a graphical comparison of measured and calculated osmolality derived from the data shown in Figure 2;

Figure 3 is a graphical representation of the correlation of osmolality to glucose, Na, and K, in a typical normal mammal;

Figure 4 is a block diagram showing a system for controlled administration of insulin that embodies the present invention;

Figure 5 is a schematic representation, partly in section, of a vapor pressure osmometer;

Figure 6 indicates the thermocouple temperature curve for the osmometer shown in Figure 5;

Figure 7 is a schematic representation of an implantable oncotic pressure osmometer;

Figure 8 is a schematic representation, partly in section, of a freezing point osmometer;

Figure 9 is a schematic representation, partly in section, of a boiling point osmometer;

Figure 10 is a schematic view of one embodiment of the present insulin infusion system including a supply reservoir, a micropump controlled by a microprocessor, and a dual channel catheter assembly for delivering insulin to the patient and providing signals to the microprocessor representing glucose levels in the patient;

Figure 11 is an enlarged cross-section of the catheter shown in Figure 10;

Figue 12 is an enlarged view of an exemplary replaceable sensor partly broken away to show interior detail;

Figure 13 is an enlarged, exploded fragmentary section of the proximal end of sensor tube of the catheter and the replaceable cap therefor;

Figure 14 is a cross-section taken generally along plane 14—14 of Figure 11 showing the catheter sensor channel and insulin channel;

Figure 15 is similar to Figure 11, and is shown here to include a secondary sensor;

Figure 16 shows the addition of a semipermeable membrane to encase the sensors;

Figure 17 is an enlarged view of a conductivity sensor partly broken away to show interior detail;

Figure 18 is an enlarged view of a ion concentration sensor partly broken away to show interior detail; and

Figure 19 is a block diagram showing a system for controlled administration of insulin using two sensors in the body.

Description of preferred embodiments

While the major effect of insulin in the mammalian body is the lowering of the blood sugar concentration, insulin can affect the concentration of a number of other body substances including potassium, phosphates, hydrogen, ketone bodies such as β-hydroxybutyrate and aceto acetate, fatty acid levels, sodium, and glycerol. In the diabetic state, the presence of many unidentified compounds is also noted, which compounds are not normal constituents of the body but which are believed to be metabolized by the body after insulin infusion. In the brain such "idiogenic osmols" can accumulate to levels of up to 40 milliosmols, and can cause cerebral edema or coma during treatment of diabetic ketoacidosis.

Osmolality is defined as the sum of the concentration of all solutes in a solution. Its units are "osmoles" or total moles of solute per kilogram of solvent. In the blood, the concentration of all chemical body substances is reflected by blood osmolality whether such substances can be chemically identified or not. It has been found that in the diabetic state, the effects of insulin infusion are reflected by a measurable change in blood osmolality and in osmolality of other body fluids. Moreover, it has been found that the detectable change in blood osmolality following exogenous and/or endogenous introduction of insulin has a greater absolute value than would be expected from the change in the blood glucose concentration. Changes in other substances such as fatty acids, glycerol, or "idiogenic osmols" are discernible by measurement of osmolality, even if such substances are not measured directly. Since the level of such substances is affected by the insulin level, variations in body insulin demand can be readily detected and accommodated so as to maintain blood osmolality within a desired range.

There may be some cases where it may be desirable to measure more than just the osmolality level. An increase in osmolality can sometimes be caused by severe physical exertion, dehydration or ingesting large amounts of certain electrolytes, e.g. table salt. While osmolality shows a good correlation with glucose levels, this correlation can sometimes be affected by these causes. Since a severely reduced level of water intake results in diminished water supply in both the intercellular and extracellular fluids, there is a resultant increase in the concentration of all metabolic substances. Such an increase can be detected by an increase in conductivity or ion concentration since the majority of extracellular osmoles are electrolytes. As the osmolality increases due to dehydration or ingestion of salt, the concentration of electrolytes increases raising the electrolytic conductivity and ion concentration. No large increase in electrolytic conductivity or ion concentration is caused by an increase in glucose or other substances controlled by insulin. By measuring the increase in conductivity or ion concentration in conjunction with the osmolality, e.g., by two separate sensing means, it is possible to "screen out" increases in osmolality not caused by increases in glucose and thus avoid an injection of insulin when it may be inappropriate. The outputs from the separate sensors may be subtracted from one another or otherwise processed, for example by using a microprocessor device so as to arrive at a control signal for dispensing insulin to the patient.

Figure 1 graphically illustrates the relationship between blood glucose concentration and blood osmolality in normal and in diabetic animals

during loss of diabetic control over a time period of one day. Dogs were the experimental animals, and alloxan was used to induce diabetes. Intravenous glucose infusion was used to increase blood glucose levels. Insulin was omitted in the diabetic animal for 24 hours so as to induce loss of diabetic control. The data points were collected over a one day period and marked changes in osmolality occurred after the infusion of glucose. The slope of the early part of blood osmolality increase is relatively steep and thus provides a sensitive indication that an insulin infusion is needed.

In Figure 1, it is seen that in a normal animal osmolality shows a weak relationship to blood glucose during the intravenous glucose infusion. Other solutes must be appearing or disappearing, to cause osmolar changes in the blood as opposed to glucose. In a diabetic animal, on the other hand, osmolality levels were already high, before glucose addition, and increased further in proportion to glucose levels between 200 and 400 mg%. The slope of increase is approximately 20 mOsm/kg per 200 mg% change in glucose concentration, approximately twice that predicted by the molecular weight of glucose alone. Accordingly, there are other solutes in the serum that contribute to this increase.

The time course of these osmolality changes is depicted in Figures 2 and 2A where various blood chemistries are depicted for one of the normal dogs. Samples were collected and insulin levels determined as set forth in the Example hereinbelow. Appropriate response of insulin to a glucose load is exhibited. It is seen that sodium, potassium, blood urea nitrogen (BUN) and protein change little during a gluclose load, but that osmolality shifts dramatically, first increasing, then decreasing. The swings in osmolality are believed to be due to changes in "unmeasured" or "idiogenic" osmoles; these osmoles are indicated by the "osmol gap" calculated by subtracting out the effects of urea, Na, anions, and glucose from total osmolality. The osmolality changes are due to glucose and to other molecules, as yet unidentified. A decrease in osmolality to a level below normal is due in part to these unidentified molecules. In a normal animal, after a glucose level increase, the pancreas functions to return osmolality to normal.

A sensor directly or indirectly responsive to osmolality changes in the body at a substantially equilibrium condition can be utilized to control the infusion of insulin and to minimize the adverse effects of diabetes. Such a sensor is sensitive to the degree of elevation of a number of important molecules besides glucose and a signal generated by the sensor controls insulin infusion, with resultant hypo-osmolality of the body stopping further dispensing of insulin. For implantation in a patient the sensor means should be compact and of relatively light weight, and preferably of a shape enabling removal through a catheter or cannula. As shown in Figures 1 and 3, osmolality is correlated with glucose, therefore control of osmolality also controls glucose.

Figure 4 schematically illustrates a closed Ip system for an effective diabetes control utilizing blood, osmolality for example, as the indicator of insulin demand. Osmolality of other body fluids is also suitable for this purpose. Transducer 11, such as an osmolality sensor, is introduced or implanted into patient 10 in any convenient manner, e.g., within patient's vascular space, subcutaneously, or intraperitoneally, so as to be in contact with a body fluid such as blood, subcutaneous fluid, peritoneal fluid, or the like. This transducer means can also be applied to body surfaces, e.g., mucosal membranes, so as to be in contact with extracellular fluid, if desired. In any case, the magnitude of the signal generated by the transducer is a function of the osmolality of the body fluid in contact therewith and is utilized to control insulin infusion from reservoir 13 via a catheter, cannula, or similar means utilizing a control unit that receives the transducer signal by electrical or mechanical means, by telemetry, or in any other convenient manner as will be discussed in detail hereinbelow. Thus, a reliable indication of the patient's insulin demand is obtained and the demand can be satisfied by infusion of the desired amount of insulin with attendant control of a variety of metabolic substances including glucose.

Osmolality alone or in conjunction with electrolytic conductivity or ion concentration may be measured in a variety of body fluids. There is rapid equilibrium between the intracellular, vascular, and interstitial components with respect to osmolality, electrolytic conductivity and ion concentration. The interstitial components are those fluids which are outside of cells and outside of the vasculature, and include peritoneal, subcutaneous, salivary, spinal fluids, and the like. A sensor for osmolality as well as for conductivity and ion concentration can be placed in contact with any of these.

The measurement of osmolality may be performed in several ways. There are four "colligative properties" of solutions, which change in proportion to osmolality: 1) vapor pressure, 2) oncotic pressure, 3) freezing point, and 4) boiling point. In each instance, the property measured is a function of the water concentration of the sample; water concentration decreases as solute concentration increases. Accordingly, preferably transducer 11 utilizes one or more of the aforementioned colligative properties to generate an output signal.

One of the most common methods of measurement of osmolality uses vapor pressure, defined as the pressure which water vapor exerts leaving the surface of a fluid. In a closed chamber, this pressure reaches equilibrium with the pressure of vapor in the gas above the fluid, and this pressure is proportional to the concentration of water in the vapor. This concentration of water may be measured conveniently by observation of the "dew point".

A typical instrument for this purpose is the Wescor Vapor Pressure Osmometer. An implantable osmometer 14 utilizing the same principle is schematically depicted in Figure 5. In this particular osmometer, a body fluid permeable membrane 15, together with housing 16 define chamber 17. In the top portion of the chamber 17 is a very small thermocouple 19. When equilibrium of vapor pressure of the body fluid and gas is attained, the thermocouple is cooled several degrees by electric current (through the Peltier effect). The electric current is then stopped, and the temperature of the thermocouple rises to the "dew point" as water condenses on the thermocouple. A typical time-temperature relationship during this procedure is shown in Figure 6. The "dew point" depression is the difference between ambient temperature and the dew point. As the vapor pressure decreases the dew point depression becomes larger. Lower vapor pressure indicates, of course, a lower concentration of water in the sample solution, that is, a higher concentration of solute (higher osmolality). Vapor pressure determination of osmolality has been found to be exceedingly sensitive and generally reliable method for measuring liquid osmolality. Osmometer 14 can be calibrated against a known standard prior to implantation, and periodically after implantation by drawing an aliquot of the patient's blood and determining the osmolality thereof extracorporeally. Alternatively, a second osmometer, similar to osmometer 14 but with a hermetically-sealed chamber containing a known gas-water vapor mixture, can be implanted to serve as a periodic calibration means.

Oncotic pressure is another possible method for determination of osmolality. Oncotic pressure is defined as the pressure exerted across a semipermeable membrane because of the presence of impermeable solutes. If a solute cannot pass through a membrane, its concentration is different on both sides of the membrane. There then exists a gradient of water concentration across the membrane. Because such membranes are usually permeable to water, there is a transfer of water across such a membrane. Such transfer will continue until pressure gradients occur to cause an equal transfer of water in the opposite direction.

An osmolality sensor utilizing oncotic pressure is shown schematically in Figure 7. A semi-permeable membrane 21, impermeable to certain solutes (such as glucose), is mounted on a rigid support 28 with a tube 25 leading to a pressure transducer 27 which can be a piezoelectric gauge or the like. Semi-permeable membrane 21, made, for example, from polysulfone film, and support 28 are positioned under the patient's skin 31 embedded in subcutaneous tissue 32. The tube and support are filled with a solvent for body fluid constituents, such as water for example. Water moves across the membrane due to the concentration differences of solutes in water, and continues to move until pressure gradients on both sides of the membrane equilibrate. The pressure gradient existing at any given time is measured utilizing a pressure gauge or differential transducer. Such pressure is proportional to the concentration of non-permeant solutes (such as glucose and/or "unmeasured osmoles") in the body fluid in contact with membrane 21.

Figure 8 schematically depicts a freezing point osmometer. Because of a variety of physical interactions of solutes with solvents, the freezing point of a solution decreases as its solute concentration increases. Thus, freezing point depression may be used to indicate osmolality of a solution. A body fluid sample is received in container 33 that is equipped with cooling coil 35. The sample is "super cooled", then made to freeze during agitation with stirrer 39. The temperature of solidification is determined using a thermocouple 37.

Figure 9 depicts yet another possibility for osmotic pressure and thus osmolality measurement, that of boiling point elevation. The device comprises vessel 41 equipped with heating coil 43 and thermocouple 45. Since increasing solute concentration results in lower solvent concentration, boiling occurs at a higher temperature. The temperature at which a body fluid sample boils is measured with thermocouple 45, the temperature elevation being effected by heating coil 43.

The vapor pressure and oncotic pressure measurements in particular may be made easily and accurately by placing the sensor in various body fluids. One particular advantage is that water is extremely diffusable, and will allow rapid equilibrium within body fluids, such as the peritoneum. For bedfast patients the osmometer can be a separate, free-standing unit operably associated with an insulin dispensing device.

For any of these osmolality sensors, the generated signal is based on an equilibrium condition, i.e., the signal is not dependent on the rate at which a physical change takes place at the transducer, but rather on the equilibrium condition that is encountered. The problems encountered by prior art sensors, due to fibrous or fibrinous deposits on the sensor or transducer, are thus obviated or at least minimized and stable, accurate readings are obtained.

An increase in osmolality caused by dehydration or salt ingestion can also be detected by an electrolyte concentration increase by measuring electrolytic conductivity or ion concentration measurements. In the case of electrolytic conductivity, the measurement can be made by placing within the body biologically inert electrodes, such as platinum, in a fixed geometric relation and measuring the resistance value across the electrodes. Improved measurements can also be made by the application of alternating current at high frequency across the electrodes. 10,000—20,000 Hertz is a useful frequency for this purpose.

Electrolytic conductivity can also be measured by means of electrical induction without the use of contacting electrodes. Such measurements are

made by inducing a current in the body fluid by use of a coil of wire. The magnitude of the inducted current which can be measured by a second coil is proportional to the conductivity of the body fluid. Instead of or in addition to conductivity, it is also possible to measure the ion concentration of the fluid.

Ion concentration can be determined by measuring the electromotive force (voltage) between two electrodes placed in the body fluid where one of the electrodes is surrounded by a membrane chosen by one knowledgeable in the art according to the body fluid constituent wished to be measured. Such measurements could include total electrolytes, particular electrolytes such as potassium or sodium, pH, and dissolved gases. In situations where there may be possible temperature variations, the measuring transducers could also include temperature compensators.

The osmolality, electrolytic conductivity and ion concentration sensors generate signals which are transmitted by means of an appropriate lead or leads, a radio signal, or similar expedients, to dispenser control means 12 which, in turn, energizes, or de-energizes, insulin dispenser 13, as indicated, for transcutaneous delivery of the requisite dose of insulin. If a separate lead or leads to the sensor are used, the conductor portion of the lead can be coated with an inert, biocompatible sheath. Optionally, a fibrous cuff, e.g., a Dacron felt or the like, can be provided around the biocompatible sheath so as to form a barrier against infections. Dispenser control means 12 can be a micro-processor, relay network, or any other switching means adapted to respond to the signal emitted by transducer means 11 and capable of energizing insulin dispenser 13. To the extent that fibrous or fibrinous deposits on a transducer may hinder the attainment of an equilibrium condition, control means 12 can include a delay means that permits energization of insulin dispenser 13 after a predetermined time period from the point in time when the signal from transducer means 11 is received. In this manner, consistent actuation of dispenser 13 can be assured as long as equilibrium can be attained at transducer means 11 within a predetermined time period. Alternatively, control means 12 can include a timing device that samples and compares signals received at predetermined intervals and energizes dispenser 13 only after differences among a plurality of received consecutive signals fall within a predetermined range.

Insulin dispenser 13 includes an insulin pool or reservoir and a pump means energizable from any convenient power source, e.g., a primary or secondary battery or gas propellant, in response to an output signal received from dispenser control 12.

Instead of an osmotic pressure measurement, the osmolality of the body fluid can also be determined using any other colligative property of the body fluid. For example, the transducer means can be adapted to measure freezing point depression, vapor pressure, or boiling point evaluation.

Likewise, control of the desired dose delivery of insulin can be effected based on electrical impedance measurements performed on the body fluid by means of implanted inert electrodes, e.g., platinum, and an alternating current generator. Electrical conductance measurements can also be used to obtain a signal suitable for controlling the infusion of insulin by means of dispenser 13.

In a method aspect of the present invention a body fluid of the patient is contacted with a transducer means that is responsive to a physical property of the body fluid, e.g., blood, which property is indicative of the patient's insulin deficiency, for example, osmolality or one of the colligative properties thereof such as vapor pressure or osmotic pressure. The transducer means is of the type that generates an output signal which is a function of the aforementioned physical property. The magnitude of the output signal generated as a consequence of the transducer means contacting the body fluid can then be utilized as an indicator of the patient's insulin requirement as well as to control the amount of insulin dispensed. Additional measurements of other body fluid properties such as electrolyte level, pH or dissolved gases by means of electrolytic conductivity or ion concentration measurements can be made, and the values thereof utilized in conjunction with the obtained osmolality value to provide a control signal to dispense the required amount of insulin. A microprocessor is well suited for this purpose.

The present invention is further illustrated by the following example.

Example

Materials and methods

Animals: Five mongrel dogs were used. Two were diabetic and three were nondiabetic. All dogs except one had a permanent indwelling catheter, the tip of which was in the cranial vena cava at the level of the second intercostal space. The canula exited from the jugular vein in the middle of the neck and was tunneled under the skin to the withers where it emerged. The free end was taped to a light harness which the dog wore all the time. One dog 17 had a temporary jugular catheter implanted before the IV glucose tolerance test.

Diabetes Induction: Diabetes was induced in two dogs (No. 17 and No. 22) with alloxan, 65 mg/kg. Dog No. 17 had been diabetic for 4 years. The other dog, No. 22, had been diabetic for 4 months. Insulin was withheld from the diabetic dogs on the day of the tests.

Glucose Tolerance Tests: Intravenous glucose tolerance tests were performed twice on each dog with the exception of the dog who had been diabetic for 4 years. Four fasting heparinized blood samples were drawn at 30 minute intervals to establish baseline values. A bolus of 50% glucose (2 ml/kg body weight) was injected via

the catheter. Blood samples were drawn at 15 minute intervals for 90 minutes and then at 30 minute intervals for one hour. Diabetic dogs were not given insulin on the day of the glucose tolerance test.

Blood samples were centrifuged in a refrigerated centrifuge at 2000G's at 5°C. for 15 minutes. Plasma was removed, aliquoted for subsequent tests and frozen.

Blood glucose was measured by the glucose oxidase-periodase method, Boehringer Mannheim Corp., Catalog No. 124036. Insulin was measured using the Beckton Dickenson insulin assay kit, Catalog No. 231517. Insulin antibodies were removed from the plasma of diabetic dogs prior to insulin assay according to the method of Nakagawa et al., Diabetes *22*: 590—600 (1973). Osmolality was measured using the Wescor vapor pressure osmometer, Model No. 5130. Sodium and potassium were analyzed by flame photometry. BUN was analyzed on the Backman BUN Analyzer II. Protein was determined using Folin Phenol reagent by the method of Lowrey et al., J. Biol. Chem. *193*: 265—275 (1951).

Data Analysis: The mean and standard error of the mean for each variable were calculated for each time period during the IV glucose tolerance test, for the normal and diabetic dogs. The data were normalized by setting the mean baseline value for each variable to zero in each test and calculating the difference between each observation and its corresponding mean baseline value. One-way analysis of variance was performed on each of the normalized variables over time to determine significance. Student-Newman-Keuls tests were performed to make multiple comparisons. A Student's t-test was used to compare the postinfusion osmole drop with baseline data. Forward least squares regression analysis was used to estimate the relationship of variables and to develop an equation for osmolality incorporating all measured variables. A stepwise regression analysis was used to pick the best set of variable to predict osmolality. A calculated value for osmolality was obtained using measurements of BUN, sodium and glucose by the formula provided by Edelman, J. S., Leibman, J., O'Meara, M. P., and Birkenfeld, L. W.: "Interrelationships between serum sodium concentration, serum osmolality and total exchangeable sodium, total exchangeable potassium and total body water". J. Clin. Invest. *37*: 1236—1256, 1958:

Osmolality=1.75 NA +0.0556 Gluclose +0.357 BUN +10.1.

The use of this value is discussed in further detail below.

Regression analyses of variance and Student-Newman-Keuls tests were performed on the Control Data Corporation's CDC 6500 computer using the Regression and One-way Programs of the Statistical Package for the Social Sciences (SPSS).

Results

Normal Dogs: Figure 2 shows the variation in several blood parameters of one normal dog (No. 27), during an IV glucose tolerance test. During the 1-1/2 hour baseline period the glucose, insulin, sodium, potassium, BUN and protein remained relatively constant. Osmolality varied within a 10 mOsmole range from 290 to 300 mOsmoles/kg. After glucose infusion, blood glucose rose from 118 to 352 mg/dl. Insulin rose from a mean baseline value of 4μU/ml to 259 μU/ml in 15 minutes and returned to the baseline by 45 minutes. Osmolality rose from the mean baseline value of 295 mOsmoles/kg to 310 mOsmoles/kg in 15 minutes. Over the next 30 minutes the osmolality dropped by 25 mOsmoles/kg to 285 mOsmoles/kg.

In the aforementioned normal dog the correlation "r" between osmolality and blood glucose was 0.80 (Figure 3). However, changes in blood glucose were not sufficient to explain the osmolality changes as the slope of this curve was greater than 1 mOsmole/180mg/L. The sodium remained relatively constant during the entire test and showed no correlation with osmolality, r=0.00. Potassium changes were inversely proportional to both osmotic pressure (r=0.64) and glucose changes (r=0.62). BUN and protein levels remained relatively constant and showed little correlation with osmotic changes (r=0.25).

The mean values for the IV glucose tolerance tests on all of the dogs are illustrated in Figure 2. During the baseline studies, the ranges in the measured variables for normal dogs were glucose: 105—110 mg/dl; osmolality 286—290 mOsmoles/kg; insulin; 17—32 μU/ml; sodium: 147—150 mEq/l; K:4.1—4.4 mEq/l; BUN: 10—12 mg/dl; plasma protein: 5.4—5.9 g/dl. After intraveneous glucose administration, glucose rose to 230 mg/dl. This represents a 12.7 mOsmoles/kg contribution to osmolality. However, during this time the mean measured osmolality rose only 9 mOsmoles/kg, and then fell to 7 mOsmoles/kg below the mean baseline level.

The maximum decrease in measured osmolality for each dog occurred from 60 to 120 minutes after glucose administration and is therefore obscured in the mean data. The magnitude of the decrease ranged from 2 to 18 mOsmoles/kg below the baseline. The mean decrease in measured osmolality after intravenous administration of glucose was 10±3 mOsmoles/kg below baseline. A Student's t-test showed this drop to be significant at the α=.05 level:

$$t^{3\,d.f.}_{\alpha=0.5}=2.352, \text{ calculated } t=2.94.$$

This decrease of osmolality below baseline cannot be explained by a drop in any specific solute below baseline levels.

Analysis of variance showed no significant differences over time in mean sodium, BUN, and protein levels after glucose infusion. The mean potassium level dropped slightly at 30 minutes, probably in response to the increase in insulin. The potassium level then rose and was

significantly (p=0.05) higher from 120 to 150 minutes.

Diabetic Dogs: Figure 1 also shows the variation in several blood parameters for one diabetic dog (No. 22) during an IV glucose tolerance test. During the 1-1/2 hour baseline period the blood glucose fell spontaneously from 544 to 436 mg/dl; measuremed osmolality varied between 306 and 310 mOsmoles/kg; sodium rose fom 126.1 to 138.0 mEq/l during the baseline period. Insulin, potassium and protein remained relatively constant both during the baseline period and after the infusion of glucose. After glucose infusion the blood glucose rose by 294 mg/dl. In 2-1/2 hours glucose returned to the initial level of 440 mg/dl. After the glucose infusion, the measured osmolality rose only 5 mOsmoles/kg above the baseline value at 15 minutes. Osmolality continued to rise at 30 minutes to 315 mOsmoles/kg even as the glucose level was decreasing. The measured osmolality then fell to a minimum of 304 mOsmoles/kg at 60 minutes. It then rose to a maximum of 322 mOsmoles/kg at 2-1/2 hours. Sodium decreased 3 mOsmoles after gluclose infusion, returned to the zero time level by 90 minutes, and then decreased again.

In this particular test the correlation between blood glucose and osmolality was very low: r=0.03. The correlation between blood glucose and osmolality in other IV glucose tolerance tests on diabetic dogs were much higher: r=0.95 and r=0.75. In this test on dog No. 22 there was a slight correlation between sodium and osmolality (r=0.24). Osmolality was inversely proportional to potassium (r=0.36), BUN (r=0.38), and protein (r=0.30), however, these correlations are low.

The mean values of the measured plasma constituents of all diabetic animals during IV gluclose tolerance tests are also shown in Figure 2. Over the baseline period, the values were: glucose, 418—439 mg/dl; sodium, 134—137 mEq/l; potassium, 4.0—4.2 mEq/l; BUN 13—15 mg/dl; protein, 5.6—5.9 g/dl. The measured osmolality over the baseline period was 297—302 mOsmoles/kg.

After glucose infusion, in diabetic dogs the mean blood glucose rose to 810 mg/dl and returned to 424 mg/dl by 2-1/2 hours. The insulin level remained relatively unchanged throughout the test. Sodium levels decreased to 133 mEq/l at 15 minutes and then increased above baseline levels reaching a maximum of 142 mEq/l at 2-1/2 hours. Potassium levels remained within the baseline range except for a 3.9 mEq/l value at 75 minutes. BUN decreased slightly showing a minimum value of 12 mg/dl at 90 minutes. Protein also showed a slight tendency to decrease after glucose infusion, reaching a minimum value at 75 minutes.

The increase in blood glucose after glucose infusion represents a 21.2 mOsmoles/kg contribution to osmolality. However, the mean measured osmolality after glucose infusion rose only 16 mOsmoles/kg above the average baseline value. It then dropped to a minimum of 301 mOsmoles/kg at 75 minutes and subsequently rose again to 309 mOsmoles/kg at 150 minutes.

After the initial rise following glucose infusion osmolality did not decrease below the baseline value in the long-term diabetic dog (No. 17). In the other diabetic dog (No. 22) the decrease was 3—6 mOsmoles/kg below baseline between 60 and 75 minutes. This decrease is not significant, however (p>.05).

In practicing the present invention, insulin can be infused as required utilizing a semi-permanently implanted percutaneous catheter, preferably of the type provided with a subcutaneously positioned fibrous cuff, made of polyester felt or similar material, that permits the ingrowth of tissue and capillary blood vessels therein. In this manner the catheter is not only fixed within the patient but also a barrier against bacterial invasion is effectively maintained.

The continuous infusion of insulin subcutaneously, intraperitoneally or into a vein in response to a change in the physical property of a body fluid provides more effective control of the patient's blood sugar level than is currently possible. Moreover, through the continuous infusion of insulin, the rate of insulin absorption is not influenced by such factors as exercise and temperature. The system can include a reservoir and a pump back adapted to be strapped to the torso of a patient at an implanted catheter, the catheter being adapted to extend under the skin down the front of the chest with the tip near the entrance to the heart in a central vein. This system can also include a wearable pack including a one-piece prefilled insulin reservoir bag. When the insulin supply becomes exhausted and must be replaced, a pump segment (the heavy tube portion which is engaged by rollers in the pump) is removed by the roller section of the pump and the pump segment of a new supply is threaded through the pump thereby eliminating the pump as a contaminant to the system.

The delivery from the pump is controlled by a microprocessor programmed to respond to an input or inputs from the implanted osmolality sensor and possibly secondary sensors and is also designed to permit the patient to anticipate the need for an extra quantity (bolus) of insulin. In the latter instance a push-button control on the side of the wearable pack can be actuated for the bolus infusion. The micro-processor can also be programmed to prevent the patient from activating the bolus injection more than a predetermined number of times a day, depending upon the physician's prescription which can be preset in the microprocessor.

In another system embodying the present invention a reservoir and pump back are adapted to be strapped to the torso of the patient. A dual channel catheter is adapted to extend under the skin (subcutaneously) down under the chest with the tip of the catheter near the entrance of a central vein. Other methods of vascular access may be employed depending on the require-

ments of the patient. Likewise, subcutaneous or peritoneal infusion of insulin may be effected. The catheter carries a cuff or sleeve of "Dacron" or other material into which the patient's tissue and blood vessels grow for permanent implantation, thereby reducing or obviatimg the possibility of bacterial infection.

The catheter itself is designed for prolonged implantation and can be constructed of a flexible silicone rubber (Silastic) or other physiologically compatible material having two parallel channels therethrough. One of these channels is the insulin infusion channel that is externally connected to the insulin pump. The other channel receives a lead wire or wires for the osmolality sensor and possible secondary sensors which project from and are positioned by the distal end of the sensor channel.

An important aspect of the present invention is that the dual channel catheter permits the removal and replacement (or removal, cleaning and replacement) of the osmolality sensor and any secondary sensor without the removal of the catheter itself. Because of fibrous or fibrinous deposits or the general degradation of the transducer means or sensors after a prolonged period of use it is necessary that they be periodically replaced or cleaned to prevent it adversely affecting the insulin delivery function. Toward this end, the external end of the catheter is split defining an insulin tube connectable to the insulin pump and a sensor tube having a releasable and removable cap through which sensor lead wires project. This cap has a conical projection that fits in and over and seals the end of the sensor tube. The cap also has a central bore therethrough that sealingly receives the sensor lead wires.

After a certain period of use, for example six months, a sensor can be replaced or cleaned, if desired, by removing the cap and withdrawing the sensor through the sensor channel and thereafter replacing the cleaned sensor or replacing it with a new sensor and cap. The position of the cap on the sensor lead wire determines the extent of projection and positioning of the sensor itself from the distal end of the sensor channel.

Referring to Figure 10, the insulin infusion system utilizing a dual lumen (channel) catheter is seen to include a replaceable insulin supply 51, small roller pump 52 controlled by a microprocessor 53 and an implanted catheter 54 connected to the insulin supply 51 through a releasable connector assembly 56. In lieu of pump 52, other types of small pumps can be used, for example a piezoelectric micropump.

While not shown in Figure 10, the insulin supply 51, small pump 52, and microprocessor 53 can be assembled into a single pack adapted to be worn by the patient in any convenient manner, e.g., strapped to the torso, or, if sufficiently small, adapted for implantation.

Insulin supply 51 is a one piece plastic insert and includas a polyethylene insulin reservoir bag 57, tube section 58, pump segment 59, and outlet tube 60 and supply connector 61, the latter forming part of the connector assembly 56. The pump segment 59 of the insulin supply can be a segment of tube section 58 or a relatively heavy-walled section 67 terminating in pump blocks 65 and 66. Heavy walled section 67 is adapted to be engaged by the rollers 55 of the micropump 52. When the insulin supply 51 is replaced, the patient discards the exhausted supply unit, threads the pump section 59 of a new supply through the pump 52, and connects connector 61 to the connector assembly 56.

The pump 52 can be a relatively small roller pump. The microprocessor 51 can be a digital logic system appropriately programmed for controlling the infusion rate of pump 52 in accordance with signals provided by osmolality sensor 70 carried intracorporeally by the catheter 54 and providing signals to the microprocessor through a lead wire 71. The details of the necessary logic in the microprocessor 53 are readily apparent to an electronics engineer of ordinary skill given the intended function so the detailed schematic therefore is not included in the drawings. Suffice it to say that the microprocessor 53 includes a variable pulse generator for driving a stepper motor associated with pump 52 at a variable rate. An input circuit in microprocessor 53 responsive to changes in signal levels in sensor lead wire 71 biases the variable pulse generator and will increase the pulse rate to the stepper motor in response to increases in the insulin demand, e.g., glucose level as sensed by sensor 70 in the patient's circulatory system and decreases the pulse rate to the pump 52 in response to decreased insulin demand sensed by sensor 70. In this manner insulin infusion rate is increased as patient's osmolality and glucose levels increase, and insulin infusion rate is decreased in response to decreased osmolality and/or glucose levels in a substantially continuous manner throughout the day.

The microprocessor 51 can also be programmed to provide automatically a higher insulin infusion rate at predetermined time periods during a 24-hour cycle, or the microprocessor can be programmed to make and store a series of insulin demand determinations at predetermined intervals, to extrapalate therefrom an anticipated peak demand, and to control insulin infusion rate accordingly.

As seen in greater detail in Figure 11, catheter 54 includes a left external section, an intermediate subcutaneous section A and an intraventricular section B. A tissue-impregnable cuff 72 surrounds the catheter 54 at the juncture of the external and subcutaneous sections to provide the cathether during prolonged implantation with an excellent bacteriological barrier. The catheter 54 includes an insulin passage 73 having a connector 74 at the end thereof adapted to be connected to connector 56 to receive insulin from pump 52. Passage 73 has a relatively narrow section 75 at its distal end that extends intravascularly.

The catheter also includes a smaller diameter

sensor channel 77 that receives the replaceable sensor lead wire 71 and positions the sensor 70 adjacent its intravascular distal end 75. The distal end 79 of the cathether passage is spaced a considerable distance from the distal end of the insulin passage 75.

The external end of the catheter 54 is split, forming an insulin tube 80 and a sensor tube 81. A replaceable cap 82 is provided for the sensor tube 81 to seal the sensor and also to permit the removal and cleaning or removal and replacement of the sensor 53 periodically to prevent fibrous or fibrinous build up or other degradation of the sensor 70 from adversely affecting the response of the microprocessor 53.

As illustrated in Figure 13, the proximal end of tube 81 has a plurality of annular integral projections 83 that hold and form a labyrinth seal with corresponding annular recesses 84 in the interior bore 85 of cap 82. To further seal sensor passage 77 from contamination, cap 82 has a cone 86 with an opening 87 therethrough that sealingly receives lead wire 71 from sensor 70. The cap 82 is positioned on the lead wire 71 at a distance so that when the sensor is replaced, the sensor head 70 will be properly positioned the desired distance from the distal end 79 of the sensor passage 77 within the patient's blood vessel.

When periodic replacement of the sensor 70 is required, cap 82 is removed and the lead wire 71 withdrawn, withdrawing sensor 70 through sensor passage 77. A temporary cap may be attached to the catheter to prevent infection in the interior. Thereafter the cleaned sensor or a new sensor 70 is inserted, with the new cap 82, and the cap replaced connected to tube 81 and to the correct position of cap 82 on wire 71. The sensor 70 is then properly positioned.

The osmolality sensor 70 as shown in Figure 12 is a vapor pressure osmometer of the type illustrated in Figure 5 and comprises a pair of matched thermocouples 91 and 93 situated in respective chambers 95 and 97. Chamber 95 is a hermetically sealed enclosure containing water vapor in equilibrium with liquid water at body temperatures. Chamber 97 is substantially the same as chamber 95 but for the fact that a wall portion 98 thereof is made of a semi-permeable membrane such as polysulfone film, cellulose acetate film, or the like, so as to permit equilibration of water vapor pressure within chamber 97 with that of the surrounding body fluid. Standard dialysis membranes that prevent the passage of the relatively smaller solute molecules but that keep out proteins are also suitable for this purpose. To minimize accumulation within the chambers between measurements, the chambers can be pressurized to drive out the substances contained therein and to permit a new equilibrium to be established prior to making the next measurement. A sterile dry air or gaseous nitrogen sweep of the chambers can also be utilized for this purpose. Thermocouple 91 in chamber 95 provides a reference value for dew point of water at the body temperature existing at the time the osmolality measurement is made. For ascertaining sodium ion concentration in the body fluid, particularly suitable is a glucose-impermeable, sodium ion-permeable cellulose acetate membrane commercially available from Osmonics Corporation, Hopkins, Minnesota, under the designation Sepa-2.

The use of two sensing transducers is shown in Figure 15 which is a modification of Figure 11. The osmolality sensor 70 and its lead 71 are as before, added are a secondary sensor 100 and its lead 99. The choice of this secondary sensor can be for conductivity or ion concentration.

The addition of semipermeable membrane capsule 101 which can be placed around the sensors shown in Figure 16. This capsule can be attached to the sensors and be withdrawn with them. In a preferred embodiment the semipermeable membrane would be impermeable to bacteria, but permeable to glucose and electrolytes and would form a seal about the distal end of the catheter 79, thus providing a second barrier against infection.

A cutaway view of the conductivity is shown in Figure 17. The sensor has an open end 104 in the casing 103 and the two electrodes 102. Fluid enters the casing, and measurements are made by measuring resistance across the two electrodes.

In Figure 18 is shown a cutaway view of an electromotive force detector with its casing 107, an open end 108, the exposed electrode 106, the sealed electrode 109 and the membrane 105. The membrane is chosen by one knowledgeable in the art depending on the body fluid constituent wished to be measured. This includes pH, total ion concentration or the concentration of particular ions such as potassium or sodium.

Figure 19 is a modification of Figure 4 to show the use of a secondary transducer 110 placed in the body 10 to provide an additional input for the microprocessor 12 which controls delivery of insulin from the reservoir 13.

The foregoing discussion and the accompanying drawings are intended as illustrative, and are not to be taken as limiting.

Claims

1. A system suitable for the administration of insulin to a patient in response to his or her insulin requirements, which system comprises an insulin dispenser (51, 52, 54) for the infusion of insulin into a patient, transducer means (70) responsive to a property of a body fluid of the patient and adapted to generate a signal having a magnitude which is a function of that property, and dispenser control means (53) to receive the signal and operably associated with the dispenser so as to deliver insulin to the patient in response to the received signal, characterized in that the transducer means (70) are responsive to the osmolality, or a colligative physical property which changes in proportion to the osmolality, of a body fluid.

2. A system in accordance with claim 1, characterised in that the physical property is the oncotic pressure, vapour pressure, freezing point or boiling point of the body fluid.

3. A system in accordance with claim 1 or claim 2, characterised in that the body fluid of the patient is blood, peritoneal fluid or subcutaneous fluid.

4. A system in accordance with any one of claims 1 to 3, characterised in that the transducer means are implantable in the patient.

5. A system in accordance with any preceding claim, characterised in that it includes a dual channel catheter (54) adapted for prolonged implantation in a patient's circulatory system, the cathether having an insulin conveying passage (73) and a sensor passage (77), pump means (52) for supplying insulin to the patient through the insulin passage (73), and a sensor (70) extending from the distal end (79) of the sensor passage (77) and having a lead (71) extending through the sensor passage (77) to provide a representation of changes in the patient's insulin demand so that the insulin delivery from the pump (52) can be varied to meet the changing needs of the patient.

6. A system in accordance with claim 5, characterised in that the distal end (79) of the sensor passage (77) terminates short of the distal end (75) of the insulin passage.

7. A system in accordance with claim 5 or claim 6, characterised in that the proximal end of the catheter (54) is separated to form an insulin tube (80) and a sensor tube (81), and a replaceable cap (82) is provided on the end of the sensor tube (81) having an opening for receiving the sensor lead (71) so that the sensor (70) and lead (71) can be periodically replaced without removal of the catheter (54) from the patient by removing the cap (82) and withdrawing the sensor (70) through the sensor passage (77) in the catheter (54).

8. A system in accordance with any one of claims 5 to 7, characterised in that a microprocessor (53) is operably connected to the pump means (52) to control the discharge from the latter, the microprocessor (53) being responsive to signals from the sensor lead (71) to vary the delivery rate of the pump means (52) in response to changes in the patient's demand.

9. A system in accordance with claim 7, characterised in that the cap (82) has a conical internal projection (86) adapted to fit sealingly within the proximal end of the sensor tube (77), the projection (86) having a central opening (87) adapted to receive the sensor lead (71).

10. A system in accordance with claim 5, characterised in that the insulin passage (73) in the catheter (54) has a substantially larger diameter than the sensor passage (77), and a tissue-impregnable cuff (72) surrounds the subcutaneous section (A) of the catheter (54).

11. A system in accordance with any preceding claim, characterised y having second transducer means which generate a signal proportional to the electrolyte concentration of the body fluid, the ion concentration of the body fluid or the electromotive force between two electrodes placed within the body.

12. A system in accordance with any one of claims 1 to 10, characterised by having a plurality of secondary transducers each set in different membranes to generate signals proportional to the concentrations of the body fluid constituents to be measured.

Revendications

1. Système convenant à l'administration d'insuline à une patient en réponse à ses besoins en insuline, lequel système comprend un distributeur d'insuline (51, 52, 54) pour l'infusion d'insuline dans un patient, des moyens transducteurs (70) sensibles à une propriété d'un fluide corporel du patient et conçus pour générer un signal ayant une amplitude qui est une fonction de cette propriété, et des moyens (53) de commande de distribution destinés à recevoir le signal et associés fonctionnellement au distributeur afin de délivrer de l'insuline au patient en réponse au signal reçu caractérisé en ce que les moyens transducteurs (70) réagissent à la molalité osmotique ou à une propriété physique colligative qui varie proportionnellement à la molalité osmotique, d'un fluid corporel.

2. Système selon la revendication 1, caractérisé en ce que la propriété physique est la pression oncotique, la pression de vapeur, le point de congélation ou le point d'ébullition du fluide corporel.

3. Système selon la revendication 1 ou la revendication 2, caractérisé en ce que le fluide corporel du patient est le sang, le fluide péritonéal ou un fluid sous-cutané.

4. Système selon l'une quelconque des revendications 1 à 3, caractérisé en ce que les moyens transducteurs sont implantables dans le patient.

5. Système selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comprend un cathéter (54) à deux canaux conçu pour une implantation prolongée dans le système circulatoire d'un patient, le cathéter présentant un passage (73) d'écoulement d'insuline et un passage (77) de capteur, des moyens de pompage (52) destinés à fournir de l'insuline au patient par le passage (73) d'insuline, et un capteur (70) partant de l'extrémité distale (79) du passage (77) du capteur et comportant un conducteur (71) s'étendant dans le passage (77) du capteur afin de fournir une représentation des variations de la demande en insuline du patient de façon que le débit d'insuline fourni par la pompe (52) puisse être modifié pour satisfaire les besoins variables du patient.

6. Système selon la revendication 5, caractérisé en ce que l'extrémité distale (79) du passage (77) du capteur aboutit à peu de distance de l'extrémité distale (75) du passage d'insuline.

7. Système selon la revendication 5 ou la revendication 6, caractérisé en ce que l'extrémité proximale du cathéter (54) est divisée de façon à former un tube (80) à insuline et un tube (81) de

capteur, et un capuchon échangeable (82) est prévu sur l'extrémité du tube (81) de capteur et présente une ouverture destinée à recevoir le conducteur (71) du capteur afin que le capteur (70) et le conducteur (71) puissent être changés périodiquement sans que le cathéter (54) soit retiré du patient, par enlèvement du capuchon (82) et retrait du capteur (70) par le passage (77) du capteur dans le cathéter (54).

8. Système selon l'une quelconque des revendications 5 à 7, caractérisé en ce qu'un microprocesseur (53) est connecté fonctionnellement aux moyens de pompage (52) pour en régler le refoulement, le microprocesseur (53) réagissant à des signaux provenant du conducteur (71) du capteur en faisant varier le débit de distribution des moyens de pompage (52) en fonction des variations de la demande du patient.

9. Système selon la revendication 7, caractérisé en ce que le capuchon (82) comporte une saillie intérieure conique (86) conçue pour s'ajuster hermétiquement dans l'extrémité proximale du tube (77) du capteur, la saillie (86) présentant une ouverture centrale (87) conçue pour recevoir le conducteur (71) du capteur.

10. Système selon la revendication 5, caractérisé en ce que le passage (73) d'insuline dans le cathéter (54) présente un diamètre sensiblement plus grand que celui du passage (77) du capteur, et un manchon (72) imprégnable en tissu entoure le tronçon sous-cutané (A) du cathéter (54).

11. Système selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comporte des seconds moyens transducteurs qui génèrent un signal proportionnel à la concentration en électrolyte du fluide corporel, la concentration ionique du fluide corporel ou la force électromotrice présente entre deux électrodes placées à l'intérieur du corps.

12. Système selon l'une quelconque des revendications 1 à 10, caractérisé en ce qu'il comporte plusieurs transducteurs secondaires placés chacun dans des membranes différentes afin de générer des signaux proportionnels aux concentrations des constituants du fluide corporel à mesurer.

Patentansprüche

1. System, das sich zur Verabreichung von Insulin an einen Patienten in Abhängigkeit von dessen oder deren Insulin-bedarf eignet, welches System eine Insulinabgabevorrichtung (51, 52, 54) zur Infusion des Insulins in einen Patienten, einen Wandler (17), der auf eine Eigenschaft einer Körperflüssigkeit des Patienten anspricht und in der Lage ist, ein Signal mit einer Größe zu erzeugen, die eine Funktion dieser Eigenschaft ist, sowie eine Abgabekontrolleinrichtung (53), die das Signal empfängt und in Wirkverbindung mit der Abgabevorrichtung steht, so daß das Insulin an dem Patienten in Abhängigkeit von dem empfangenen Signal abgegeben wird, umfaßt, dadurch gekennzeichnet, daß der Wandler (70) auf die Osmolalität anspricht oder auf eine konzentrationsbedingte physikalische Eigenschaft, die in Abhängigkeit von der Osmolalität einer Körperflüssigkeit sich ändert.

2. System nach Anspruch 1, dadurch gekennzeichnet, daß die physikalische Eigenschaft der oncotische Druck, der Dampfdruck, der Gefrierpunkt oder der Siedepunkt der Körperflüssigkeit ist.

3. Systen nach Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß die Körperflüssigkeit des Patienten Blut, Peritonalflüssigkeit oder eine subkutane Flüssigkeit ist.

4. System nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß der Wandler in den Patienten implantierbar ist.

5. System nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß es einen Zweikanalkatheter (54) umfaßt, der auf eine längere Implantation in dem Kreislauf eines Patienten abgestellt ist, wobei der Katheder einen Insulintransport-Durchgang (73) und einen Sensor-durchgang (77), eine Pumpeinrichtung (52) zur Zufuhr des Insulins zu dem Patienten durch den Insulindurchgangs- (73) und einen Sensor (70) der sich von dem distalen Ende (79) des Sensordurchgangs (77) erstreckt und eine Leitung (71) umfaßt, die sich durch den Sensordurchgang (77) erstreckt, aufweist, um eine Wiedergabe der Änderungen des Insulinbedarfs des Patienten zu ermöglichen, so daß die Insulinsufuhr von der Pumpe (52) so variiert werden kann, daß sie dem sich ändernden Bedarf des Patienten entspricht.

6. System nach Anspruch 5, dadurch gekennzeichnet, daß das distale Ende (79) des Sensordurchgangs (77) kurz vor dem distalen Ende (75) des Insulindurchgangs endet.

7. System nach Anspruch 5 oder Anspruch 6, dadurch gekennzeichnet, daß das Proximalende des Katheters (54) getrennt ist, um einem Insulinschlauch (80) und einen Sensorschlauch (81) zu bilden, und eine auswechselbare Kappe (82) an dem Ende des Sensorschlauchs (81) vorgesehen ist, der eine Öffnung zur Aufnahme der Sensorleitung (71) aufweist, so daß der Sensor (70) und die Leitung (71) ohne Entfernung des Katheters (54) aus dem Patienten periodisch ausgetauscht werden können, indem die Kappe (82) entfernt und des Sensor (70) durch den Sensordurchgang (77) in den Katheter (54) zurückgezogen wird.

8. System nach einem der Ansprüche 5 bis 7, dadurch gekennzeichnet, daß ein Mikroprozessor (53) in Wirkverbindung an die Pumpeinrichtung (52) angeschlossen ist, um die Ausströmmenge der letzteren zu kontrollieren, wobei der Mikroprozessor (53) auf die Signale der Sensorleitung (71) anspricht, um die Ausströmgeschwindigkeit der Pumpeinrichtung (52) in Abhängigkeit von den Änderungen des Bedarfs des Patienten zu variieren.

9. System nach Anspruch 7, dadurch geekennzeichnet, daß die Kappe (82) einen konischen Innenvorsprung (86) aufweist, der dichtend in dem Proximalende des Sensorschlauchs (77)

sitzt, wobei der Vorsprung (86) eine mittlere Öffnung (87) aufweist, die die Sensorleitung (71) aufnimmt.

10. System nach Anspruch 5, dadurch gekennzeichnet, daß der Insulindurchgang (73) in dem Katheter (54) einen wesentlich größeren Durchmesser als der Sensordurchgang (77) aufweist und eine gewebeimprägnierbare Manschette (72) den subkutanen Abschnitt (A) des Katheters (54) umgibt.

11. System nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß ein zweiter Wandler vorgesehen ist, welcher ein Signal proportional zu der Elektrolytkonzentration der Körperflüssigkeit, der Ionenkonzentration der Körperflüssigkeit oder der elektromotorischen Kraft zwischen zwei Elektroden, die in dem Körper angeordnet sind, erzeugt.

12. System nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß ene Vielzahl von sekundären Wandlern vorgesehen ist, die jeweils in unterschiedlichen Membranen angeordnet sind, um Signale zu erzeugen, die proportional zu den Konzentrationen der zu messenden Körperflüssigkeitsbestandteile sind.

Fig. 1.

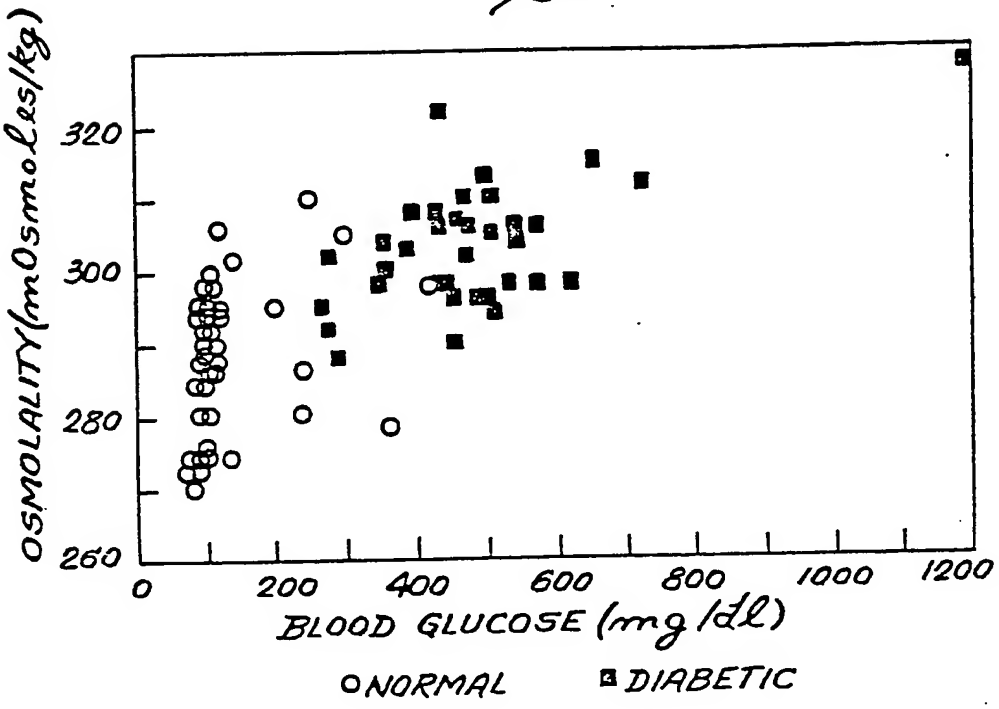
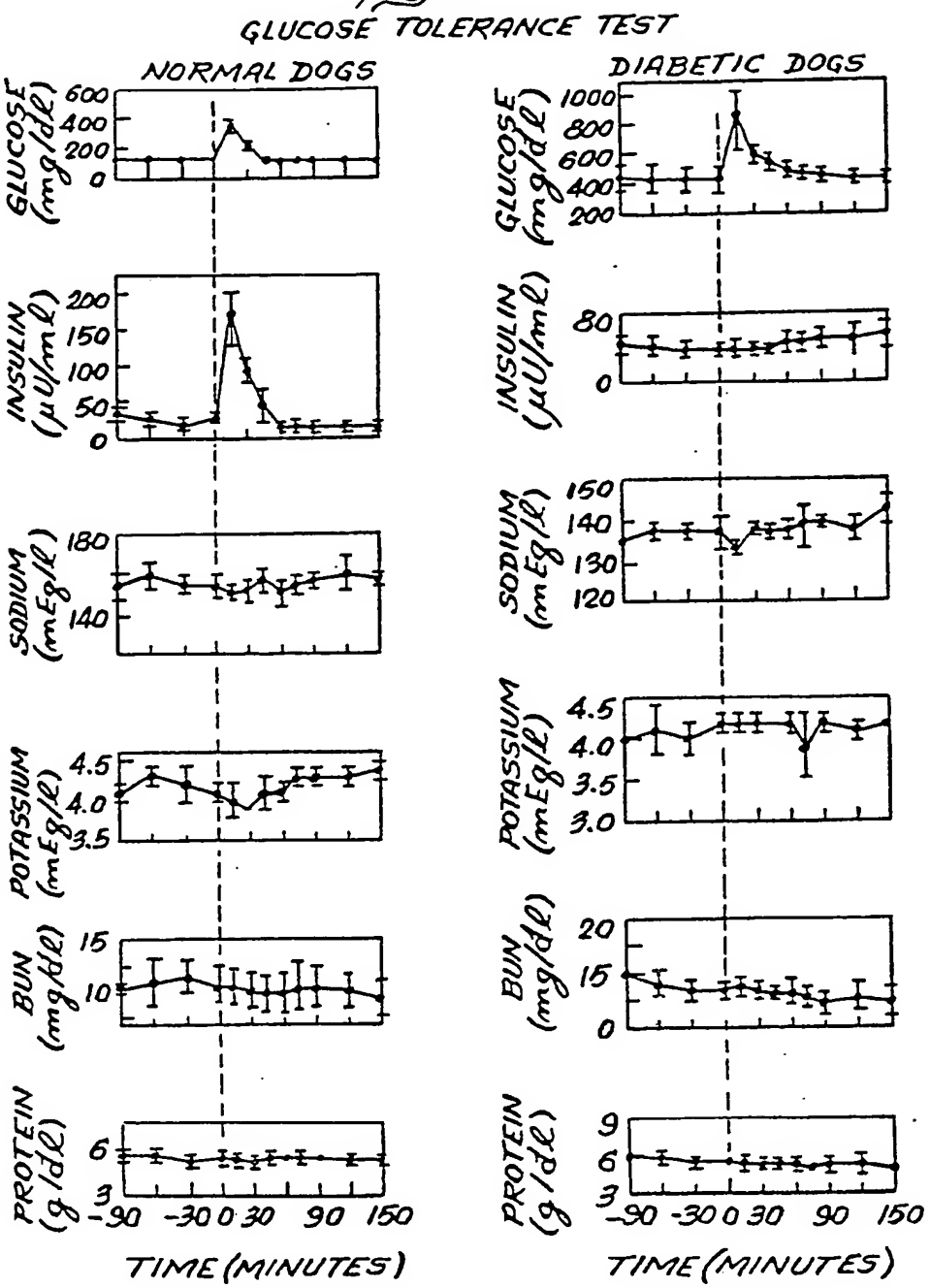

OSMOLALITY (mOsmoles/kg)
320
300
280
260
0
200
400
600
800
1000
1200
BLOOD GLUCOSE (mg/dl)
NORMAL
DIABETIC

FIG. 2.


GLUCOSE TOLERANCE TEST
NORMAL DOGS
DIABETIC DOGS
GLUCOSE (mg/dl)
INSULIN (μU/ml)
SODIUM (mEg/l)
POTASSIUM (mEg/l)
BUN (mg/dl)
PROTEIN (g/dl)
TIME (MINUTES)

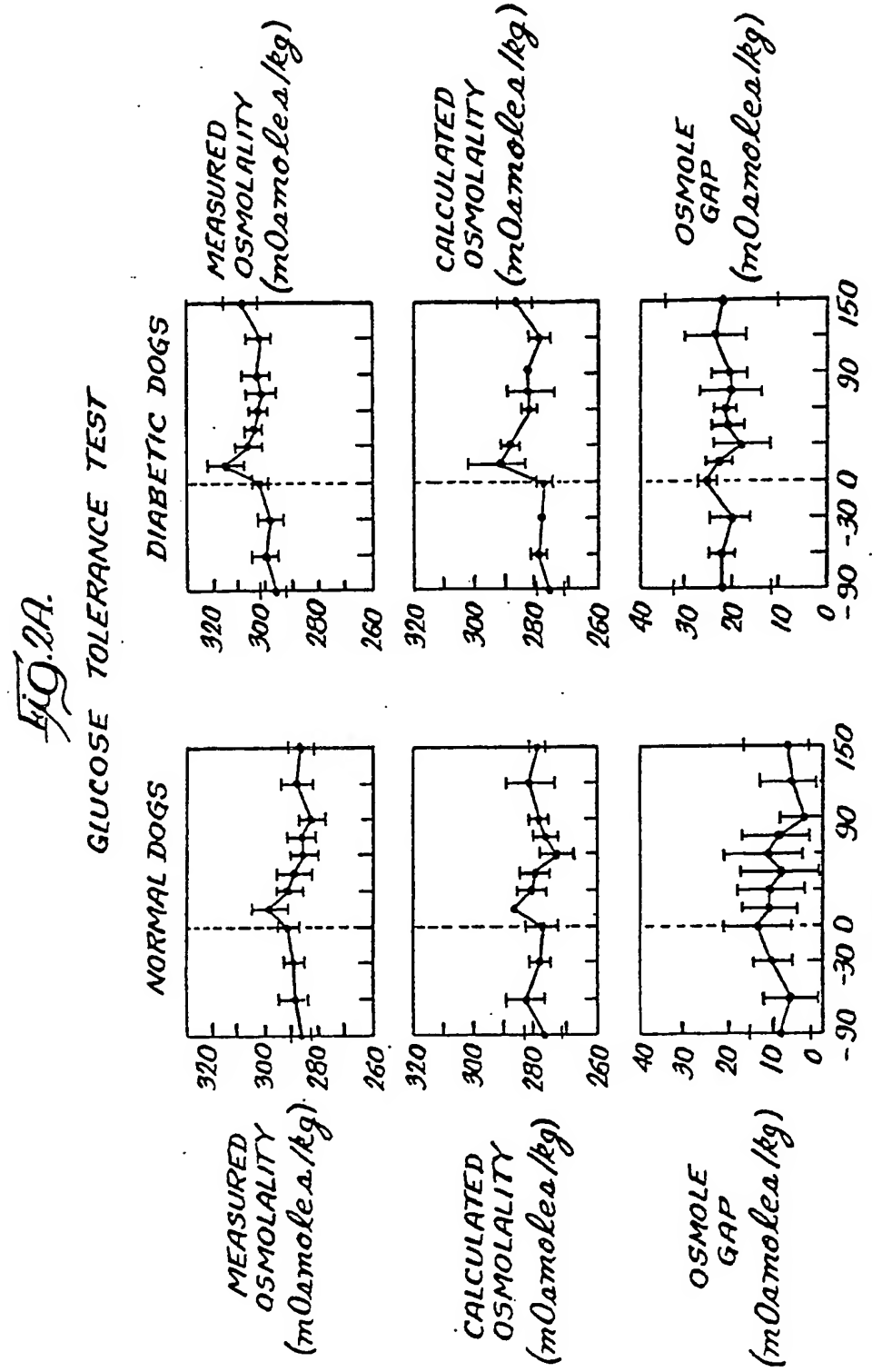


FIG.2A.
GLUCOSE TOLERANCE TEST
NORMAL DOGS
DIABETIC DOGS
MEASURED OSMOLALITY (mOsmoles/kg)
CALCULATED OSMOLALITY (mOsmoles/kg)
OSMOLE GAP (mOsmoles/kg)
320
300
280
260
40
30
20
10
0
-90
-30
0
90
150
TIME (MINUTES)

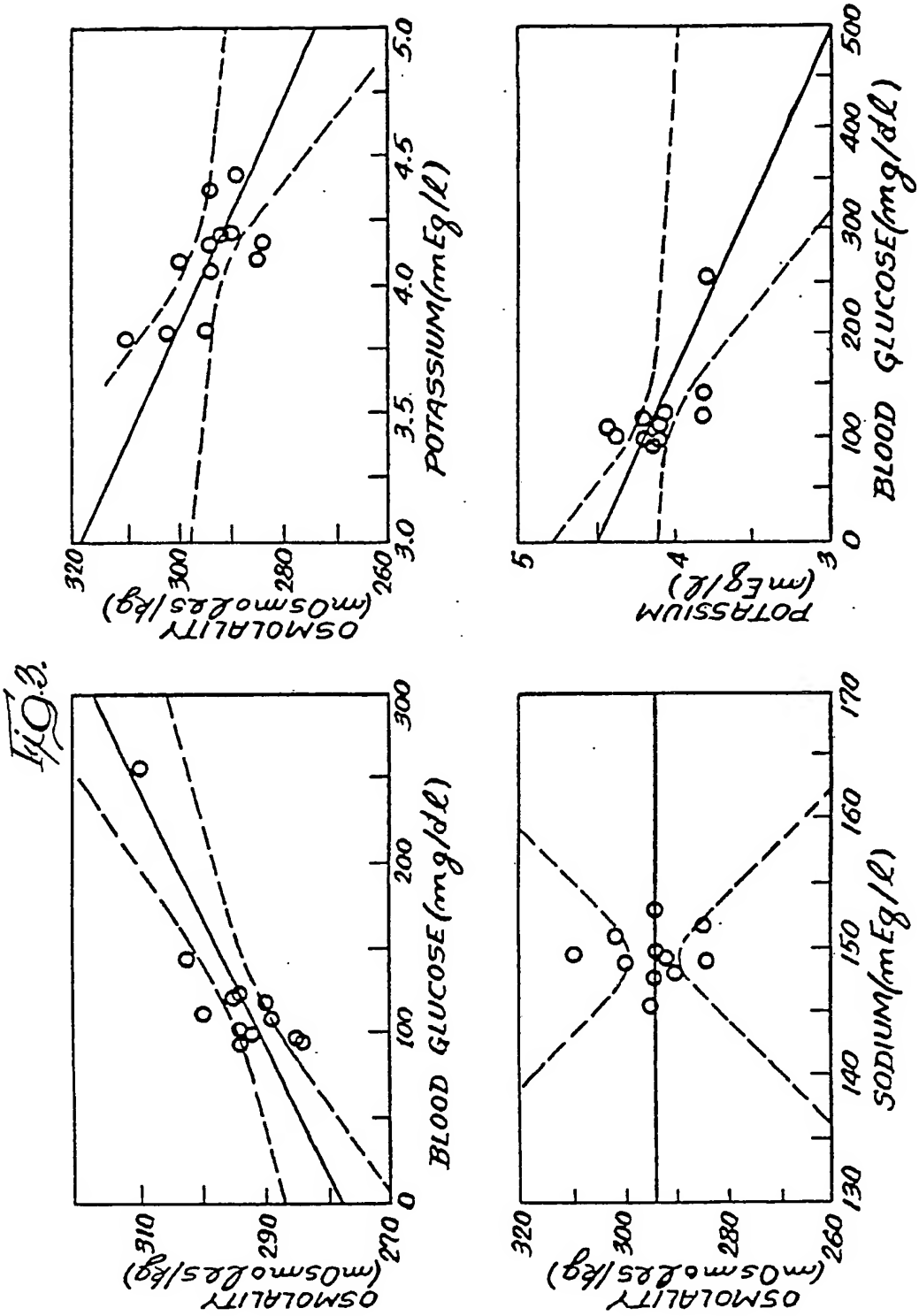

OSMOLALITY (mOsmoLes/kg)
320
300
280
260
POTASSIUM (mEq/l)
5
4
3
BLOOD GLUCOSE (mg/dl)
0
100
200
300
400
500
OSMOLALITY (mOsmoLes/kg)
320
300
280
260
SODIUM (mEq/l)
130
140
150
160
170
OSMOLALITY (mOsmoLes/kg)
310
290
270
BLOOD GLUCOSE (mg/dl)
0
100
200
300
OSMOLALITY (mOsmoLes/kg)
320
300
280
260
POTASSIUM (mEq/l)
3.0
3.5
4.0
4.5
5.0

Fig.3.

Fig.4.

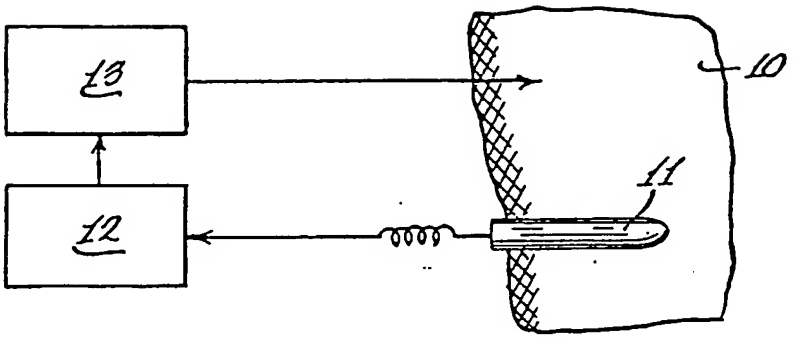


Fig.5.

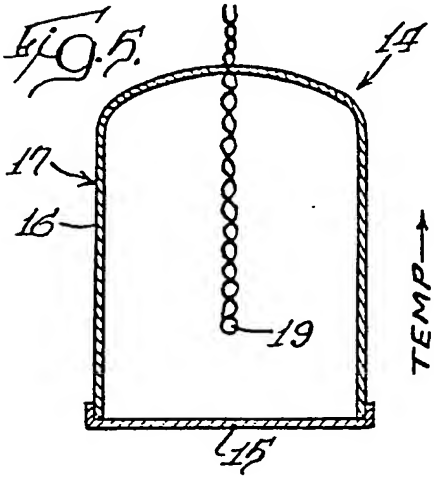


Fig.6.

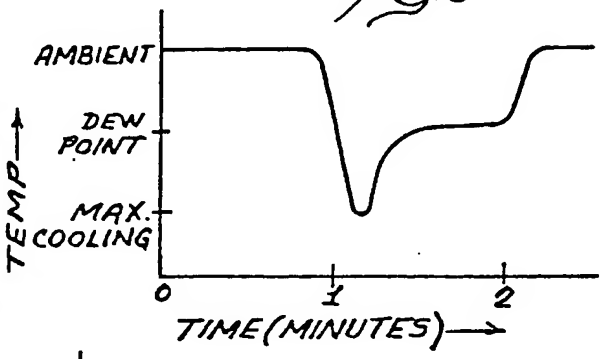


Fig.7.

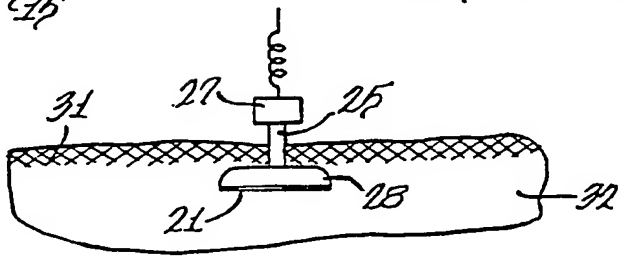


Fig.8.

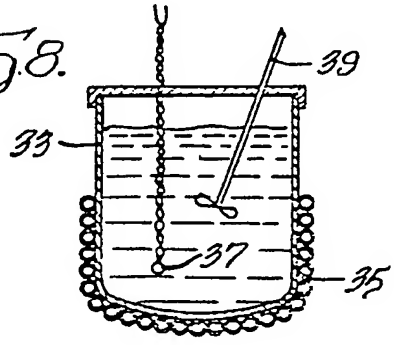
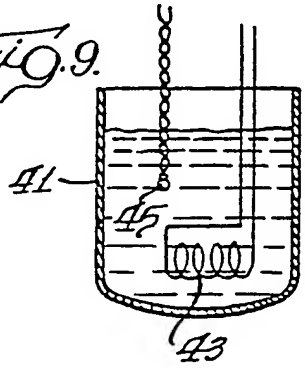
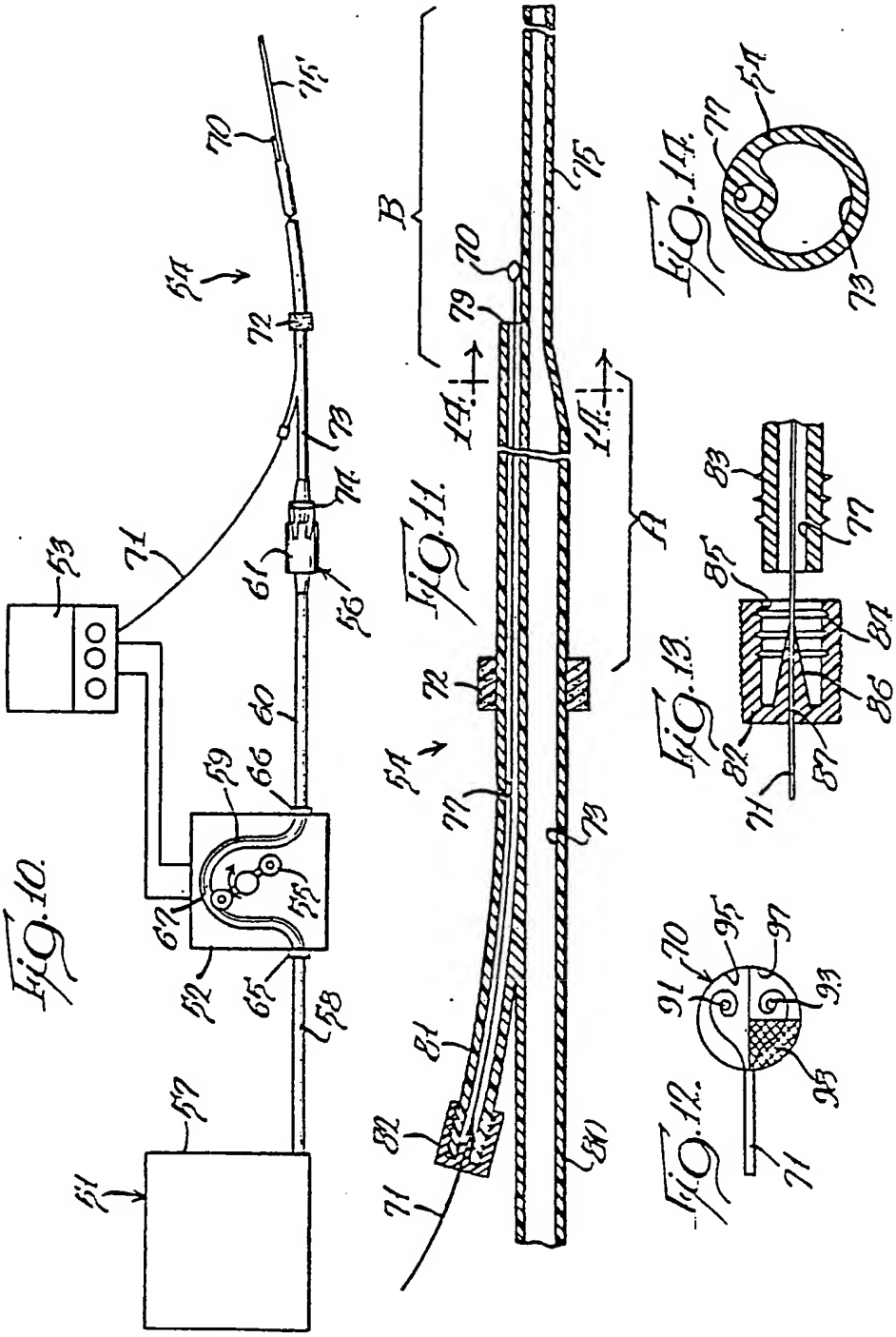


Fig.9.





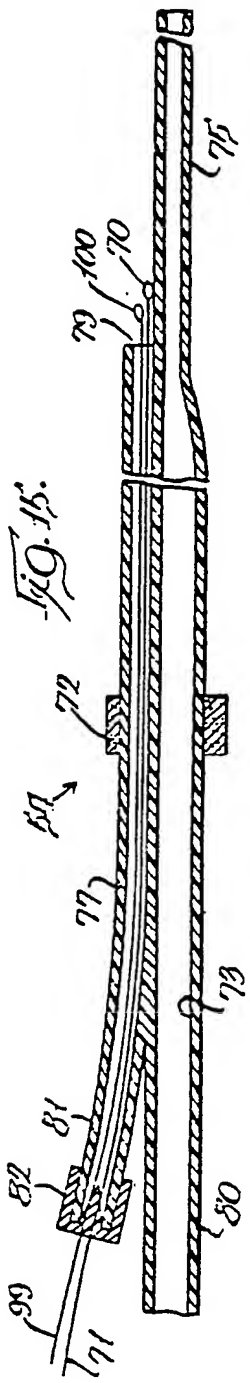


Fig. 15.

Fig. 16.

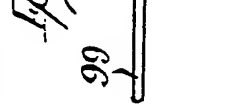


Fig. 17.

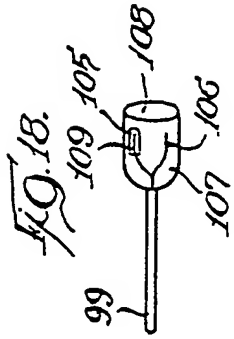


Fig. 18.

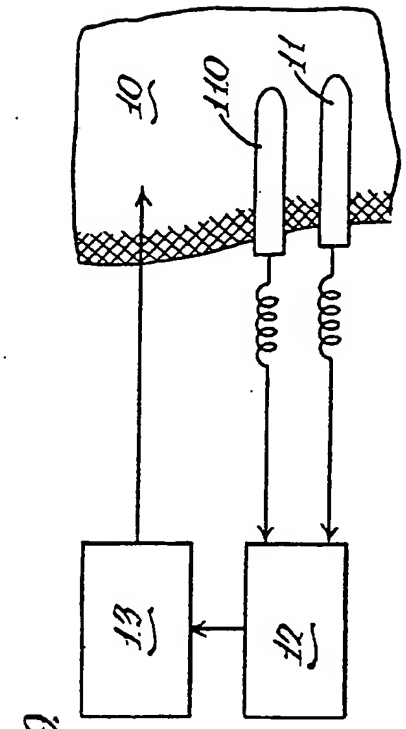


Fig. 19.